

Express Mail Label Number :  
EM192718124US

Date of Deposit: October 15, 1997

**REQUEST FORM FOR FILE WRAPPER CONTINUING APPLICATION UNDER 37 CFR 1.62**

Attorney's Docket Number <b>10254/7008</b>	Anticipated classification of this application Class          Subclass	Prior Application  Examiner D. Lukton Art Unit 1811
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Date of Deposit: October 15, 1997

TO: **BOX FWC**  
**ASSISTANT COMMISSIONER FOR PATENTS**  
**WASHINGTON, D.C. 20231**

This is a request for filing a ☐ Continuation-in-part ☒ Continuation ☐ Divisional Application under 37 CFR 1.62 of prior application Serial No. 08/459,654, filed on June 2, 1995, entitled INHIBITORS OF DIPEPTIDYL-AMINOPEPTIDASE TYPE IV by the following named inventor(s).

FULL NAME OF INVENTOR	FAMILY NAME Bachovchin	FIRST GIVEN NAME William	SECOND GIVEN NAME W.
RESIDENCE & CITIZENSHIP	CITY Melrose	STATE/FOREIGN COUNTRY MA	CITIZENSHIP USA
POST OFFICE ADDRESS	P.O. ADDRESS 71 Warwick Road	CITY Melrose	STATE/ZIP/COUNTRY MA 02176, USA
FULL NAME OF INVENTOR	FAMILY NAME Plaut	FIRST GIVEN NAME Andrew	SECOND GIVEN NAME G.
RESIDENCE & CITIZENSHIP	CITY Boston	STATE/FOREIGN COUNTRY MA	CITIZENSHIP USA
POST OFFICE ADDRESS	P.O. ADDRESS 750 Washington Street	CITY Boston	STATE/ZIP/COUNTRY MA 02111, USA
FULL NAME OF INVENTOR	FAMILY NAME Flentke	FIRST GIVEN NAME George	SECOND GIVEN NAME R.
RESIDENCE & CITIZENSHIP	CITY Boston	STATE/FOREIGN COUNTRY MA	CITIZENSHIP USA
POST OFFICE ADDRESS	P.O. ADDRESS 136 Harrison Avenue	CITY Boston	STATE/ZIP/COUNTRY MA 02111, USA

The above-identified prior application in which no payment of the issue fee, abandonment of, or termination of proceedings has occurred, is hereby expressly abandoned as of the filing date of this new application. Please use all the contents of the prior application file wrapper, including the drawings, as the basic papers for the new application. (Note 37 CFR 1.60 may be used for applications where the prior application is not to be abandoned.)

1. ☐ Enter the amendment previously filed on \_\_\_\_\_ Under 37 CFR §1.116 but unentered, in the prior application.

2. ☒ A preliminary amendment is enclosed.

The filing fee is calculated on the basis of the claims existing in the prior application as amended at 1 and 2 above.

#### CLAIMS AS FILED

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
TOTAL CLAIMS	19	-20 = 0	X \$ =	\$ 0
INDEPENDENT CLAIMS	3	-3 = 0	X \$ =	\$ 0
MULTIPLE DEPENDENT CLAIMS (if applicable) (37 CFR 1.16 (d))				= \$
BASIC FEE				= \$ 395.00
<b><u>TOTAL FILING FEE:</u></b>				= \$ 395.00

3. ☒ The Commissioner is hereby authorized to:

- ☒ charge any deficiency in the enclosed fees which may be required or credit any overpayment in the enclosed fees to Deposit Account 23/2825. A duplicate copy of this sheet is enclosed.
- ☐ charge any fees which may be required under 37 C.F.R. §1.16 and §1.17 to deposit Account No. 23/2825. A duplicate copy of this sheet is enclosed.

4. ☒ A check in the amount of \$395.00 is enclosed.

5. ☐ A new oath or declaration is included since this application is a continuation-in-part which discloses and claims additional matter.

6. ☒ Amend the specification by inserting before the first line the sentence:

This application is a ☐ continuation-in-part, ☒ continuation, ☐ division of application Serial No. 08/459,654, filed June 2, 1995.

7. ☒ A verified statement to establish small entity under 37 CFR 1.9 and 1.27 ☐ is enclosed.  
☒ was filed in a prior application and such status is still proper and desired (37 CFR 1.28(a)).

8. ☐ Priority of application Serial No. \_\_\_\_\_, filed on \_\_\_\_\_ in \_\_\_\_\_ is claimed under 35 U.S.C. 119.

9. [x] The prior application is assigned of record to New England Medical Center Hospital, Inc., and Trustees of Tufts College.

10. [x] Also enclosed: Copy of Petition for Three Month Extension of Time in prior application U.S.S.N. 08/459,654.

11. [x] The power of attorney in the prior application is to:

David Wolf, Reg. No. 17,528; George L. Greenfield, Reg. No. 17,756; Stanley Sacks, Reg. No. 19,900; Edward F. Perlman, Reg. No. 28,105; Lawrence M. Green, Reg. No. 29,384; Steven J. Henry, Reg. No. 27,900; Therese A. Hendricks, Reg. No. 30,389; Edward R. Gates, Reg. No. 31,616; William R. McClellan, Reg. No. 29,409; Ronald J. Kransdorf, Reg. No. 20,004; M. Lawrence Oliverio, Reg. No. 30,915; James J. Foster, Reg. No. 30,052; Charles E. Pfund, Reg. No. 17,030; Jason M. Honeyman, Reg. No. 31,624; James H. Morris, Reg. No. 34,681; Peter C. Lando, Reg. No. 34,654; Gary S. Engelson, Reg. No. 35,128; Peter J. Gordon, Reg. No. 35,164; Randy J. Pritzker, Reg. No. 35,986; Richard F. Giunta, Reg. No. 36,149; Douglas R. Wolf, Reg. No. 36,971; Elizabeth R. Plumer, Reg. No. 36,637; Timothy J. Oyer, Reg. No. 36,628; John N. Anastasi, Reg. No. 37,765; Brett N. Dorny, Reg. No. 35,860; Helen C. Kindregan, Reg. No. 39,248; James M. Hanifin, Jr., Reg. No. 39,213; David E. Huang, Reg. No. 39,229; Christopher S. Schultz, Reg. No. 37,929; Paul D. Sorkin, Reg. No. 39,039; Douglas C. Daskocil, Reg. No. 39,660; John R. Van Amsterdam, Reg. No. 40,212; Scott A. Ouellette, Reg. No. 38,573; Matthew B. Lowrie, Reg. No. 38,228; Jodi-Ann McLane, Reg. No. 36,215; Michael G. Verga, Reg. No. 39,410; Robert E. Rigby, Jr., Reg. No. 36,904; Robert A. Skrivaneck, Jr., Reg. No. 41,316; Robert M. Abrahamsen, Reg. No. 40,886; Lesley A. Hamlin, Reg. No. 41,054; Lindsay G. McGuinness, Reg. No. 38,549; Mike W. Crosby; Reg. No. P-40,970; c/o Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210, Tel: (617) 720-3500.

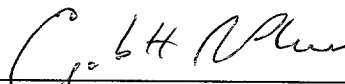
- a.[x] The power (copy enclosed, submitted 10/15/97) appears in the original papers in the prior application.
- b.[ ] Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.
- c.[x] A new power has been executed and is attached.
- d.[x] Address all future communications: (May only be completed by applicant, or attorney or agent of record)

Elizabeth R. Plumer  
Wolf, Greenfield & Sacks, P.C.  
600 Atlantic Avenue  
Boston, MA 02210  
Tel: (617) 720-3500

It is understood that secrecy under 35 U.S.C. 122 is hereby waived to the extent that if information or access is available to any one of the applications in the file wrapper of a 37 CFR 1.62 application

be it either this application or a prior application in the same file wrapper, the Patent and Trademark Office may provide similar information or access to all the other applications in the same file wrapper.

15 October 1997  
Date

  
Elizabeth R. Plumer - Reg. No. 36,637

Person signing is:

- ☐ Inventor(s)
- ☐ Assignee of complete interest
- ☒ Attorney or agent of record
- ☐ Filed under 37 CFR §1.34(a)

Registration number if acting under 37 CFR 1.34(a) \_\_\_\_\_

Rev. 10/05/94

Date of Deposit: October 15, 1997

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ATTORNEY'S DOCKET NO: I0254/7008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: William W. Bachovchin et al.  
Serial No: Unknown  
Filed: Herewith  
For: INHIBITORS OF DIPEPTIDYL-AMINOPEPTIDASE TYPE IV

BOX FWC  
Assistant Commissioner for Patents  
Washington, D.C. 20231

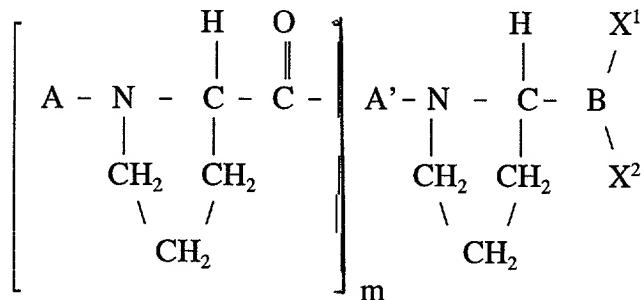
Dear Sir:

PRELIMINARY AMENDMENT

In the Claims:

Please amend claim 13 as follows:

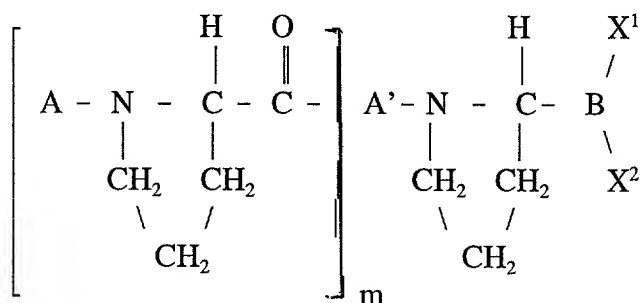
13. (Twice Amended) An inhibitor of DP-IV, having the structure:



wherein m is an integer between 0 and 10, inclusive; A and A' are L-amino acid residues such that the A in each repeating bracketed unit can be a different amino acid residue; the C bonded to B is in the L-configuration; the bonds between A and N, A' and C, and

between A' and N are peptide bonds; and each X<sup>1</sup> and X<sup>2</sup> is, independently, a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group at physiological pH. Please add the following new claims:

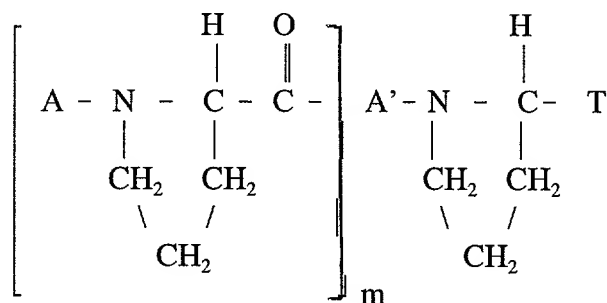
21. The inhibitor of claim 13, wherein m is 0.
22. The inhibitor of claim 13, wherein m is an integer between 1 and 10, inclusive.
23. A substantially pure preparation of an inhibitor of DP-IV, said inhibitor having the structure:



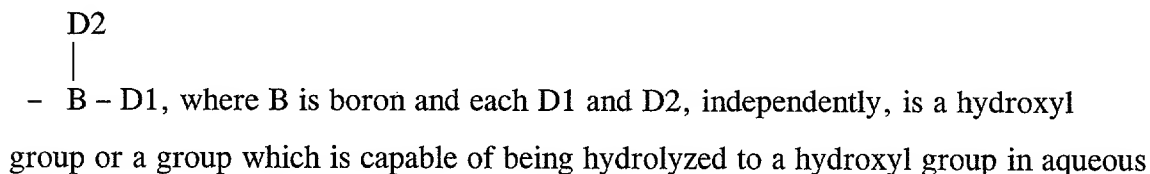
wherein m is an integer between 0 and 10, inclusive; A and A' are L-amino acid residues such that the A in each repeating bracketed unit can be a different amino acid residue; the C bonded to B is in the L-configuration; the bonds between A and N, A' and C, and between A' and N are peptide bonds; and each X<sup>1</sup> and X<sup>2</sup> is, independently, a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group at physiological pH.

24. The preparation of claim 23, wherein said inhibitor is 99% pure.
25. The preparation of claim 23, wherein A and A' of said inhibitor are independently proline or alanine residues.

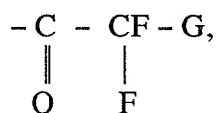
26. The preparation of claim 23, wherein m is 0.
27. The preparation of claim 23, wherein m is an integer between 1 and 10.
28. The preparation of claim 23, wherein X<sup>1</sup> and X<sup>2</sup> are hydroxyl groups.
29. The preparation of claim 23, wherein said inhibitor is L-Ala-L-boroPro.
30. The preparation of claim 23, wherein said inhibitor is L-Pro-L-boroPro.
31. An inhibitor of DP-IV, having the structure:



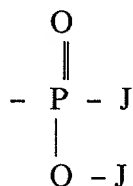
wherein m is an integer between 0 and 10, inclusive; A and A' are L-amino acid residues such that the A in each repeating bracketed unit can be a different amino acid residue; the C bonded to B is in the L-configuration; the bonds between A and N, A' and C, and between A' and N are peptide bonds; each X<sup>1</sup> and X<sup>2</sup> is, independently, a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group at physiological pH; and wherein T is selected from the group consisting of the formula:



solution at physiological pH; a group of the formula:



where G is either H, F or an alkyl group containing 1 to 20 carbon atoms and optional heteroatoms which can be N, S, or O; and a phosphonate group of the formula:



where each J, independently, is O-alkyl, N-alkyl, or alkyl, each said O-alkyl, N-alkyl or alkyl comprising 1 - 20 carbon atoms and, optionally, heteroatoms which can be N, S, or O; said T being able to form a complex with the catalytic site of a dipeptidyl-aminopeptidase type IV (DP-IV) enzyme.

32. The inhibitor of claim 31, wherein T is a phosphonate group.

33. The inhibitor of claim 31, wherein T is a trifluoroalkyl ketone group.

34. A method for inhibiting a DP-IV comprising,

contacting said DP-IV with an inhibitor of claim 31 under conditions to permit binding of said inhibitor to said DP-IV.

#### REMARKS

Claim 13 is amended to reinstate the claim language prior to the Amendment filed on February 26, 1997 in the parent case, USSN 08/459,654, by Applicants' prior attorneys of record.



New claims 22-34 are added.

New claims 22 and 23 are dependent upon claim 13. New claim 22 is identical to original claim 15 in USSN 08/459,654 (which had been canceled in the prior application). New claim 23 includes a limitation which further limits the value of m in the claim 13 structure.

New claim 24 is directed to a "substantially pure preparation of an inhibitor of DP-IV" which has the structure of amended claim 13. Support for this new claim is found at least on page 21 (line 12) which describes the purification procedure that was used to obtain "an isomeric purity of about 99-6% for each isomer".

New claim 25 is directed to the preparation of claim 24 with the further limitation that the inhibitor is present at 99% purity. Support for this new claim also is found on page 21.

New claims 25-30 parallel original claims 14-18 and new claim 23 which further specify limitations of the DP-IV inhibitor. Accordingly, support for these claims is found at least in original claims 14-18 as filed.

Claim 31 is directed to the structure of claim 13 which has been modified to include a carboxyl terminal functional group which is selected from the groups consisting of the boronates (the subject matter of claim 13), the phosphonates (the subject matter of new claim 32), and the trifluoroalkyl ketones (the subject matter of new claim 33). Support for new claims 31, 32, and 33 is found at least beginning on page 5 of the specification which describes the different types of T groups that can be present at the C terminal end of the molecule.

Claim 34 is directed to a method for inhibiting DP-IV which involves contacting DP-IV with the inhibitor of claim 31 under conditions to permit binding of the inhibitor to the DP-IV. Support for this new claim is found at least in original claim 11 as filed.

No new matter has been added.

Remarks Concerning the Outstanding Rejections in the Parent Case, USSN 08/459,654

The following information is provided to expedite the prosecution of this file wrapper continuation of USSN 08/459,654:

Applicants are in the process of compiling a complete list of references which may be relevant to the subject matter that is claimed in this pending application. These references were identified in related patent applications or were identified in general searches of the literature and patent databases. Applicants shall make this information of record within three months of filing this file-wrapper-continuation. Not all of the references cited may be prior art with respect to the claimed invention, i.e., certain references may have been published after the earliest effective filing date of this pending file-wrapper-continuation application. In addition, certain of the references may have been filed within one year of the filing of the earliest effective application to which priority is claimed and, therefore it is possible that a declaration under 37 C.F.R. §1.131 could remove certain references as prior art. For example, Applicants have evidence available to submit in the form of a section 1.131 Declaration for the purpose of removing as prior art, the reference by W. Bachovchin, et al., in J. Biol. Chem. 265(7):3738 (1990), which describes certain DP-IV isomers. This information will be provided upon request by the Examiner.

Applicants have added new claims to inhibitors of DP-IV and methods of using said inhibitors. Certain of the new claims define the purity of the originally claimed DP-IV inhibitor (claim 13); other claims define DP-IV inhibitors in which the carboxyl terminal group contains a functional group which is a boronate groups (as in original claim 13), a phosphonate group or a trifluoroalkyl ketones. Applicants respectfully request that the Examiner consider the patentability of these new claims. Support for the new claims is provided in the specification on the pages identified above.

The undersigned attorney has noted the objection to the Abstract's length and content. Amendment to the Abstract will be made after Applicants have had an opportunity to consider the Examiner's Office Action in response to the newly added

claims.

The following comments are specifically directed to the outstanding claim rejections in the parent application.

A rejection of claims under 35 U.S.C. §112(1) in USSN 08/459,654 appears to be based on “scientific reasoning”, namely, that a non-conservative amino acid substitution at positions A or A’ in the formula of claim 13 would result in a “loss of activity” . Applicants note that the pending claims do not specify a particular *level* of activity, merely a composition which is in a particular isomeric form. That compounds which fall within the claim may have different *levels* of activity is not a sufficient basis to reject the claim for a lack of enablement. Moreover, Applicants have in their possession experimental or other evidence to support their position that DP-IV inhibitors will tolerate a broad spectrum of substitutions for amino acids in positions A and A’ of claim 13. Upon request by the Examiner, Applicants will provide this information in the form of a declaration under 35 U.S.C. §1.132 to expedite the prosecution of this continuation.

With respect to the rejection of claims under 35 U.S.C. §112(2) in USSN 08/459,654, it is believed that this rejection is obviated by the amendments submitted herewith.

The pending claims of USSN 08/459,654 also were rejected under 35 U.S.C. §102(e) as anticipated by Bachovchin (US Patent No. 4,935,493). This rejection is based upon an interpretation that the Bachovchin patent is “silent as to the stereochemical disposition of the  $\alpha$ -carbon” and, accordingly, that Bachovchin shows the L-isomer. Respectfully, Bachovchin is *not* silent as to the stereochemical disposition of this carbon atom. Rather, Bachovchin clearly states (column 7, lines 67-68): “all natural amino acids are in the L-configuration. H-boroProline is in the D, L-configuration”. Accordingly, Bachovchin does not teach a substantially pure preparation of the structure of amended claim 13 but, rather, Bachovchin teaches a racemic mixture.

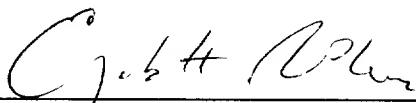
Respectfully , one would expect that a mixture which contains 100% of an active compound would be approximately twice as active as a mixture which contains only 50% of the active compound (a racemic mixture). In contrast to such expectations, the specification (page 21, line 29) discloses that the inhibition constant for the L-isomer of proBoroPro was approximately *three orders of magnitude* better than the D-isomer for this same dipeptide. This difference was pointed out in the Amendment filed on February 26, 1997 by Applicants' former representative. Compounds which have such unexpected properties are, by their nature, inherently nonobvious. For this additional reason, it is believed that the Bachovchin patent does not teach, suggest, or render obvious the invention as now claimed.

#### SUMMARY

Applicants which to expedite the prosecution of this application. Accordingly, if the Examiner feels that a telephone conference would be helpful, he is respectfully requested to call the undersigned attorney at the telephone number presented below.

It is believed that the rejections of record in the parent application, USSN 08/459,654, are not applicable to the pending claims. Accordingly, it is respectfully requested that favorable action on the new claims be taken.

Respectfully submitted,



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Elizabeth R. Plumer

Reg. No. 36,637

WOLF, GREENFIELD & SACKS, P.C.

600 Atlantic Avenue

Boston, Massachusetts 02210

Tel: (617) 720-3500

Attorney's Docket No. I0254/7008

Date: October 15, 1997

xNDD

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ATTORNEY'S DOCKET NO. 10254/7008 (ERP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: William Bachovchin, et al.  
Serial No: unknown (file wrapper continuation of USSN 08/459,654, filed June 2, 1995)  
Filed: October 15, 1997  
For: INHIBITORS OF DIPEPTIDYL-AMINOPEPTIDASE TYPE IV

ASSISTANT COMMISSIONER FOR PATENTS  
WASHINGTON, D.C. 20231

Sir:

POWER OF ATTORNEY

The undersigned, TRUSTEES OF TUFTS COLLEGE, owner of the interest conveyed by W. Bachovchin and G. Flentke in the above-identified patent application (a file wrapper continuation of serial no. 08/459,654, filed June 2, 1995), filed October 15, 1997, hereby appoints:

David Wolf	17,528	Peter C. Lando	34,654	Paul D. Sorkin	39,039
George L. Greenfield	17,756	Gary S. Engelson	35,128	Douglas C. Doskocil	39,660
Stanley Sacks	19,900	Peter J. Gordon	35,164	John R. Van Amsterdam	40,212
Edward F. Perlman	28,105	Randy J. Pritzker	35,986	Scott A. Ouellette	38,573
Lawrence M. Green	29,384	Richard F. Guinta	36,149	Matthew B. Lowrie	38,228
Steven J. Henry	27,900	Douglas R. Wolf	36,971	Jodi-Ann McLane	36,215
Therese A. Hendricks	30,389	Elizabeth R. Plumer	36,637	Michael G. Verga	39,410
Edward R. Gatz	31,616	Timothy J. Oyer	36,628		
William R. McClellan	29,409			Robert E. Rigby, Jr.	36,904
Ronald J. Kransdorf	20,004	John N. Anastasi	37,765		
M. Lawrence Oliverio	30,915	Brett N. Domy	35,860	Robert A. Skrivaneck, Jr.	41,316
James J. Foster	30,052	Helen C. Kindregan	39,248	Robert M. Abrahamsen	40,836
Charles E. Pfund	17,030	James M. Hanifin, Jr.	39,213	Lesley A. Hamlin	41,054
		David E. Huang	39,229	Lindsay G. McGuinness	38,549
Jason M. Honeyman	31,624			Mike W. Crosby	P-40,970
James H. Morris	34,681	Christopher S. Schultz	37,929		

of Wolf, Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, Massachusetts 02210-2211, as applicant's attorneys with full power of substitution and revocation to take any and all action necessary with regard to the above-identified application.

Address all telephone calls to Elizabeth R. Plumer, at telephone no. (617) 720-3500. Please forward all correspondence to:

Elizabeth R. Plumer  
Registration No. 36,637  
Wolf, Greenfield & Sacks, P.C.  
Federal Reserve Plaza  
600 Atlantic Avenue  
Boston, MA 02210-2211

Please charge any fee or any fee deficiency occasioned by this document to Deposit Account No. 23/2825.

Respectfully submitted,

Date: 10/15/97

By: Joseph J. Byrne  
Signature

Joseph J. Byrne, Ph.D.

Associate Provost for Research

Date of Deposit: October 15, 1997

ATTORNEY'S DOCKET NO. 10254/7008 (ERP)  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: William Bachovchin, et al.  
Serial No: unknown (file wrapper continuation of USSN 08/459,654, filed June 2, 1995)  
Filed: October 15, 1997  
For: INHIBITORS OF DIPEPTIDYL-AMINOPEPTIDASE TYPE IV

ASSISTANT COMMISSIONER FOR PATENTS  
WASHINGTON, D.C. 20231

Sir:

POWER OF ATTORNEY

The undersigned, NEW ENGLAND MEDICAL CENTER HOSPITALS, INC., owner of the interest conveyed by Andrew G. Plaut in the above-identified patent application (a file wrapper continuation of serial no. 08/459,654, filed June 2, 1995), filed October 15, 1997, hereby appoints:

David Wolf	17,528	Peter C. Lando	34,634	Paul D. Sorkin	39,039
George L. Greenfield	17,756	Gary S. Engelson	35,128	Douglas C. Doskocil	39,660
Stanley Sacks	19,900	Peter J. Gordon	35,164	John R. Van Amsterdam	40,212
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Lawrence M. Green	29,384	Richard F. Guinta	36,149	Matthew B. Lowrie	38,228
Steven J. Henry	27,900	Douglas R. Wolf	36,971	Jodi-Ann McLane	36,215
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Edward R. Gates	31,616	Timothy J. Oyer	36,628		
William R. McClellan	29,409			Robert E. Rigby, Jr.	36,904
Ronald J. Kransdorf	20,004	John N. Anastasi	37,765		
M. Lawrence Oliverio	30,915	Brett N. Dorny	35,860	Robert A. Skrivaneck, Jr.	41,316
James J. Foster	30,052	Helen C. Kindregan	39,248	Robert M. Abrahamson	40,886
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		David E. Huang	39,229	Lindsay G. McGuinness	38,549
Jason M. Honeyman	31,624			Mike W. Crosby	P-40,970
James H. Morris	34,681	Christopher S. Schultz	37,929		

of Wolf, Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, Massachusetts 02210-2211, as applicant's attorneys with full power of substitution and revocation to take any and all action necessary with regard to the above-identified application.

Address all telephone calls to Elizabeth R. Plumer, at telephone no. (617) 720-3500. Please forward all correspondence to:

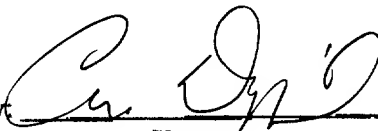
Elizabeth R. Plumer  
Registration No. 36,637  
Wolf, Greenfield & Sacks, P.C.  
Federal Reserve Plaza  
600 Atlantic Avenue  
Boston, MA 02210-2211

Please charge any fee or any fee deficiency occasioned by this document to Deposit Account No. 23/2825.

Respectfully submitted,

Date: 10/15/97

By:

  
Signature

\_\_\_\_\_  
Christopher Dippel

\_\_\_\_\_  
Director, Technology Transfer